REMARKS/ARGUMENTS

Claims 82, 84-96 and 98-122 are pending in the application. Claims 82, 87, 88, 90, 93, 96, 98, 100 and 102 had been withdrawn as a result of an earlier restriction requirement and have now been canceled. Claim 114 has also been canceled. Claim 111 has been amended to correct an obvious typographical error. Claim 108 has been amended to claim a particular embodiment of the invention; support for this amendment can be found in the specification, for example, on page 25, line 34 through page 26, line 1. New claims 123-141 have been added.

Applicants acknowledge with appreciation the withdrawal of the previous rejections of claims 118 and 119 under 35 U.S.C. §112 and the withdrawal of the rejections of claims under 35 U.S.C. § 103(a) (Office Action, page 2). Applicants also acknowledge with appreciation the rejoinder of claims 84-86 with the pending claims (Office Action of 26 May 2006, page 2). Due to the rejoinder of claim 84, claim 122 has been cancelled as being essentially duplicative of the claim 84 subject matter (see, *e.g.*, discussion of claim 122 in previously submitted Amendment).

Claim 101 has been amended for clarification, and new claims 123-141 have been added. Support for this amendment and for the new claims can be found in the specification as filed, as further discussed in detail below.

No new matter has been added by way of amendment. Reexamination and reconsideration of the claims are respectfully requested.

Claim 110 Meets the Requirements of 35 U.S.C. §112, First Paragraph

Claim 110 stands rejected for failing to meet the written description requirement. Applicants respectfully traverse this rejection.

The Office Action concludes (page 3, top of page) that the specification and the claims as originally filed do not provide support for the invention as now claimed. Applicants believe that support for claim 110 is provided by the specification and claims as previously discussed. Nevertheless, solely in order to expedite prosecution, claim 110 has been amended to recite that the cell aggregates are subcultured one to five times. Support for this amendment can be found, for example, in the original claims, particularly original claim 28, which recites "[t]he method according to claim 21 wherein the cell aggregates of step (e) are serially subcultured one to five times." Note that original claim 21 recites "[a] method of producing a population of mature

dendritic cells from proliferating cell cultures" and that step (e) requires "serially subculturing the cell aggregates one or more times to enrich the proportion of dendritic cell precursors."

In view of the amendment to claim 110 and the support discussed above, Applicants respectfully submit that this rejection has been overcome and should be withdrawn.

The Non-Statutory Double-Patenting Rejection

The Office Action (page 3, #7) has provisionally rejected claims 84-86, 89, 91-92, 94-95, 99, 101 and 103-122 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 45 and 46 of the copending and later filed U.S. Patent Application No. 10/287,813.

Applicants respectfully traverse this rejection and note that claims 114 and 122 have been canceled. The Office Action acknowledges (page 4, first paragraph) that Applicants have requested that this ground for rejection be held in abeyance until allowable subject matter is indicated.

The Claims Meet the Requirements of 35 U.S.C. §112, First Paragraph

The Office Action has rejected claims 84-86, 89, 91-92, 94-95, 99, 101, and 103-122 under 35 U.S.C. § 112, first paragraph (Office Action of 26 May 2006, page 4, #8). Applicants note that claim 122 has been canceled and respectfully traverse this rejection with regard to the remaining claims.

As an initial matter, Applicants again note the comment reproduced in the Office Action (page 4, last full paragraph) that claim 101 changed between 7/09/01 and 4/12/02, "apparently without amendment." Applicants note, as discussed in the Amendment filed March 10, 2006, that claim 101 was amended as indicated in a Preliminary Amendment filed on 3 January 2002. In addition, claim 101 is amended herein for clarification. Support for this amendment is further discussed below.

The Office Action concludes that the rejected claims fail to meet the written description requirement because the specification and claims as originally filed do not provide support for the invention as now claimed. The Office Action particularly points to claims 101 and 120 and

states (page 4, #8) that "no support for the limitations of these claims as they are now recited has been submitted. Limitations have been added amendment by amendment such that the claimed invention has evolved into one that is not supported by the specification." Applicants respectfully disagree with this conclusion and traverse the rejection. A discussion of the support provided in the specification is provided below.

Applicants believe that the specification and original claims adequately support the claims in their present form. At present, claim 101 (as currently amended) and claim 120 are as follows:

> 101. (Currently Amended) An *in vitro* composition comprising antigen-activated dendritic cells presenting fragmented antigen and derived from an *in vitro* culture of an enriched and expanded population of proliferating dendritic cell precursors by a method comprising:
>
> providing a tissue source comprising dendritic cell precursors;
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> optionally treating the tissue source comprising dendritic cell precursors to increase the proportion of dendritic cell precursors;
>
> culturing the tissue source on a substrate in a culture medium comprising GM-CSF to obtain cell aggregates comprising proliferating dendritic cell precursors; and
>
> subculturing the cell aggregates at least one time to enrich the proportion of dendritic cell precursors;
>
> wherein the dendritic cell precursors are cultured *in vitro* in the presence of an antigen for a time sufficient to allow the antigen to be fragmented and presented.

> 120. (Previously Presented) An *in vitro* composition comprising antigen-activated dendritic cells, wherein said antigen-activated dendritic cells are derived from an *in vitro* culture of a population of enriched and expanded proliferating precursor cells which were contacted *in vitro* with antigen in the presence of GM-CSF for a sufficient time for antigen fragmentation and presentation to occur.

In the previously submitted Amendment, Applicants described some of the support in the specification for the pending claims. This discussion is summarized below. However, Applicants note that the current Office Action seems to emphasize a number of distinctions (*e.g.*, between "mature DCs" and "antigen-activated DCs") as though these are exclusive and unrelated concepts. However, they are not. While various aspects of the invention may be subject to restriction for examination purposes, this artificial fragmentation cannot then be imposed to rewrite the specification or to fragment the description into unintelligible pieces. Statements

regarding various aspects of the invention must be read in the context of the application. The specification must be read as a coherent whole, as it was written, and not artificially subdivided by the Examiner into a series of isolated and unrelated statements.

Particularly, the Office Action imposes a number of subdivisions on the subject matter that are not present in the specification. For example, the Office Action discusses "antigen-activated DCs" and "mature DCs" as if they were completely different entities with no properties in common. The Office Action states, for example (page 5) that "[p]ages 40 and 19 disclose antigen-activated DCs, but not antigen-activated DCs prepared by the method of the instant claims." However, this conclusion ignores what is clear from the description and would be obvious to one of skill in the art—that these DCs share many properties and that therefore aspects of the description which are applicable to one are often applicable to the other. The Office Action seems to require a specification in which every variation of each aspect of the invention is described verbatim in its entirety. This is not the correct standard. Indeed, a verbatim description of every detail of each aspect of the invention would require an application of enormous proportions, and one that would certainly be objected to by the PTO for excessive length. Rather, the specification should be evaluated for the applicable standard that it reasonably conveys to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. Applicants believe that the specification, when properly read as a whole, clearly provides support for the claims.

Moreover, Applicants believe that the Office Action does not set forth a *prima facie* case of lack of written description by "providing reasons why a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed...." (see MPEP §2163.04(I)(B)). The present Office Action does not do this in view of the specification as a whole. In reviewing the specification, it should be kept in mind that "the disclosure as originally filed does not have to provide *in haec verba* support for the claimed subject matter...." (see *Purdue Pharma L.P. v. Faulding, Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000)), as the Office Action seems to require.

For example, Applicants disagree with the conclusions reached on page 5 of the Office Action that the claims are not adequately supported by the specification. Independent claims 101 and 120 (and therefore also the rest of the claims, which either depend from or incorporate the

limitations of claim 101 or 120) are drawn to antigen-activated dendritic cells derived from a culture of proliferating dendritic cell precursors[1] and produced by a method comprising exposure to GM-CSF. The first paragraph of the Detailed Description (page 19, lines 25-31) states that "[t]his invention relates to a method of producing **cultures of proliferating dendritic cell precursors** which mature ***in vitro*** to mature dendritic cells. The **dendritic cells and the dendritic cell precursors produced according to the method** of the invention may be produced in amounts suitable for various immunological interventions for the prevention and treatment of disease." The specification further states that these dendritic cells **can be activated with antigens to provide antigen-activated dendritic cells**[2]. The specification states that "[a]nother embodiment of the invention [is] **antigen-activated dendritic cells prepared according to the method of the invention** ..." (page 9, line 35 through page 10, line 3). In this manner, the specification teaches antigen-activated dendritic cells prepared by the methods of the invention.

As discussed in the specification, antigen-activated dendritic cells are dendritic cells that are prepared according to the methods of the invention and are further (*i.e.*, ***additionally***) treated by exposure to antigen. That is, "**[a]ntigen-activated dendritic cells [can be] prepared according to the method of the invention** in which antigen-activated dendritic cells have been exposed to antigen and express modified antigens for presentation to and activation of T cells" (specification at page 9, line 35 through page 10, line 3; see also independent claim 120, which requires that the antigen-activated dendritic cells are derived from a population of proliferating precursor cells). In other words, the methods of the invention are equally applicable to "antigen-activated dendritic cells," but additional steps beyond the standard methods are necessary to produce these activated cells. Accordingly, one of skill will appreciate that discussion in the specification of methods of producing dendritic cells are also used to produce antigen-activated dendritic cells. For these reasons, Applicants disagree with the conclusion in the Office Action

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1 Applicants note that the Office Action dated 3 February 2004 (at part 10) acknowledged that the specification provides support for "an enriched and expanded population of dendritic cell precursors."

2 "The present invention provides for the first time a method of obtaining dendritic cells in sufficient quantities to be used to treat or immunize animals or humans with **dendritic cells which have been activated with antigens**" (specification at page 40, lines 25-28). "Another embodiment of the invention [is] **antigen-activated dendritic cells prepared according to the method of the invention** in which antigen-activated dendritic cells have been exposed to antigen and express modified antigens for presentation to and activation of T cells" (specification at page 9, line 35 through page 10, line 3). "**Antigen-activated dendritic cells** and dendritic cell modified antigens may both be used to elicit an immune response against an antigen" (specification at page 42, lines 9-11).

(page 5) that the cited passages which discuss the preparation of dendritic cells are not also applicable to the preparation of antigen-activated dendritic cells.

Antigen fragmentation and presentation are also discussed in the specification. Independent claim 101 is drawn to a composition comprising antigen-activated dendritic cells presenting fragmented antigen. Independent claim 120 is drawn to a composition comprising antigen-activated dendritic cells derived from precursor cells which were contacted *in vitro* with antigen in the presence of GM-CSF for a sufficient time for antigen fragmentation and presentation to occur. The specification states that "[i]t is also an object of this invention to provide dendritic cell precursors capable of phagocytosing antigenic material to be processed and **presented** by the dendritic cell precursors" (see page 12, lines 26-29). The specification discusses the surprising advantages of exposing dendritic cell precursors to antigen and the superior qualities of dendritic cells derived from these precursors. Specifically, the specification states (on page 35, line 34 through page 36, line 15) that:

> Mature dendritic cells, while effective in sensitizing T cells to several different antigens, show little or no phagocytic activity. To the extent that endocytosis is required for antigen processing and presentation, it was not previously evident how dendritic cells would present particle-associated peptides. **Based on our work, it is now evident that progenitors to dendritic cells which this invention provides can internalize such particles for processing and presentation**. The types of particles which may be internalized by phagocytosis include bacteria, viral, mycobacteria or other infections agents capable of causing disease. Accordingly, any antigenic particle which is internalized and processed by the dendritic cell precursors of this invention is also suitable for making the various immunogens, toleragens and vaccines described as part of this invention. **Processing of antigen by dendritic cells or dendritic cell precursors includes the fragmentation of an antigen into antigen fragments which are then presented**.

The specification further discusses on page 37, lines 4-19, that different and superior dendritic cells are obtained via the methods of the invention. Particularly, the specification discusses that populations of cells produced by a method of the invention are enriched for dendritic cells that have internalized particles to which they were exposed and which are "much more potent in presenting antigens to primed T cells than corresponding cultures of mature dendritic cells that

are exposed...." Antigen presentation by DCs is also discussed generally on page 5, line 27 through page 6, line 9, and additional discussion of antigen fragmentation can be found in the specification on page 5, lines 23-30 and on page 6, lines 4-32. See also working Example 3 (beginning on page 65) which describes the production of dendritic cell progenitors (see, *e.g.*, page 65, lines 15-29) that phagocytosed latex particles (see, *e.g.*, Figure 12A and page 68, line 20 through page 69, line 14) and BCG mycobacteria (see, *e.g.*, Figure 13 and page 69, lines 16-34) to which they were exposed. The cells that had been exposed to BCG mycobacteria then presented them to T cells, as illustrated by assays *in vitro* (see, *e.g.*, Figure 15 and page 71, line 20 through page 72, line 11) and *in vivo* (see, *e.g.*, Figures 16 and 17 and page 72, line 12 through page 73, line 19).

In this manner, the specification provides support for the derivation of antigen-activated dendritic cells from a population of proliferating precursor cells as well as for the fragmentation and presentation of antigen. Accordingly, Applicants respectfully request that the rejection of claims on this basis (see Office Action, page 4, #8) be withdrawn.

The methods of the invention taught in the specification include the methods specified in the claims. Thus, for example, claim 101 includes a step of "providing a tissue source comprising dendritic cell precursors," and the specification teaches that "[t]he starting material for the method of producing dendritic cell precursors and mature dendritic cells is a **tissue source comprising dendritic cell precursors** which precursor cells are capable of proliferating and maturing *in vitro* into dendritic cells when treated according to the method of the invention" (page 19, line 32 through page 20, line 2). Claim 101 further includes a step of "optionally treating the tissue source comprising dendritic cell precursors to increase the proportion of dendritic cell precursors." The specification states that "the **tissue source may be treated** prior to culturing to enrich the proportion of dendritic precursor cells relative to other cell types" (page 20, line 33 through page 21, line 6). Applicants appreciate the acknowledgment of this support in the Office Action (page 5, fourth paragraph from bottom).

Applicants believe that claim 101 as previously pending was supported by the specification. However, in order to advance prosecution and for clarification, claim 101 has been amended and now specifies a step of "culturing the tissue source on a substrate in a culture medium comprising GM-CSF to obtain cell aggregates comprising proliferating dendritic cell

precursors." Claim 120 recites antigen-activated dendritic cells derived from a population of proliferating precursor cells which were contacted *in vitro* with antigen in the presence of GM-CSF. The culture of cells in culture medium supplemented with GM-CSF is discussed, for example, on page 24, lines 3-7[3]. The specification teaches that "**GM-CSF** has surprisingly been found to promote the **proliferation** *in vitro* of precursor dendritic cells. Cells are cultured in the presence of GM-CSF at a concentration sufficient to promote the survival and proliferation of dendritic cell precursors" (see page 25, lines 19-26). Under these culture conditions, cell aggregates form which eventually give rise to dendritic cells (see, *e.g.*, page 28, lines 21-27[4] and page 27, lines 20-24[5]). Subculturing is discussed, for example, on page 28, lines 9-11[6] and page 29, line 20 through page 30, line 3.

Applicants again note, as discussed above, that the Office Action (page 5) does not appear to have considered the specification as a whole. The Office Action concludes that the different portions of the specification are discussing separate inventions. This is not correct. The compositions and methods of the invention are described in detail, which necessarily takes the format of discussing various aspects of the compositions and methods separately in order to completely describe each aspect. Thus, for example, page 26 of the specification largely describes the use of GM-CSF and results obtained with actual working examples, the first half of page 27 largely describes various other cytokines that may be used in the methods of the invention, and the second half of page 27 through page 30 discuss culturing of the cells. However, this does not mean that each of these pages is describing a separate invention, as the Office Action seems to imply. Rather, the specification must be read as a whole. Applicants believe that when the specification is read as a whole, it provides ample support for the claimed invention.

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[3] Page 24, lines 3-7 are as follows: "Cells obtained from treatment of the tissue source are cultured to form a primary culture on an appropriate substrate in a culture medium supplemented with GM-CSF or a GM-CSF derivative...."

[4] Page 28, lines 21-27 are as follows: "Cells are incubated for a sufficient time to allow the surface of the culture dish to become covered with a monolayer of tightly adherent cells including macrophages and fibroblasts affixed to which are aggregates of nonadherent cells. At this time, any nonadherent cells are removed from the wells, and the **cellular aggregates** are dislodged for subculturing."

[5] Page 27, lines 20-24 are as follows: "The primary cultures from the tissue source are allowed to incubate at about 37°C under standard tissue culture conditions of humidity and pH until a population of cells has adhered to the substrate sufficient to allow for the separation of nonadherent cells."

[6] Page 28, lines 9-11 are as follows: "The nonadherent cells from the primary culture are subcultured by transferring them to new culture flasks at a density sufficient to allow for survival of the cells...."

Claims 101 and 120 (and therefore the rest of the claims, which depend from or incorporate the limitations of claims 101 and 120) require that the dendritic cell precursors are cultured *in vitro* in the presence of an antigen for a time sufficient to allow the antigen to be fragmented and presented. This limitation is supported, for example, on page 36, lines 30-32, which state that "[c]ells should be exposed to antigen for **sufficient time to allow antigens to be internalized and presented** on the cell surface." Presentation of antigens is further discussed, for example, on page 39, lines 16-18, which states that "[a]n important feature of the dendritic cells of this invention is the capacity to efficiently present microbial and other antigens on both class I and II products."

For the above reasons, Applicants believe that the specification teaches the methods of the invention as presently claimed. Thus, Applicants disagree with the conclusion(s) in the Office Action (page 5) that the specification does not provide support for the present claims. Applicants respectfully request that the rejection of claims on this basis be withdrawn.

Applicants note that new claims 123-141 have been added. In order to facilitate examination of these claims, Applicants here discuss in detail the support for these newly added claims in the specification as filed. Because these newly added claims are supported by the specification as filed, Applicants respectfully request that these newly added claims not be rejected for lack of written description.

New independent claim 123 is similar to claim 101 as amended and contains additional limitations regarding the number of cells in the composition and regarding the tissue source. Particularly, claim 101 requires that the composition comprise at least 1×10^6 dendritic cells. Support for this limitation can be found in the specification, for example, in working Example 1 on page 46, lines 9-19. This working example describes the production using a method of the invention of at least 1×10^6 cells from cultures derived from a single donor[7]. Further support for dendritic cell yields within this range obtained using a method of the invention is provided in working Example 6, page 78, lines 3-9, which describes the isolation of $6 - 12 \times 10^6$ cells from individual human donors.

[7] Ten subcultures from a single donor each comprising at least 10×10^4 dendritic cells would provide a total of at least 100×10^4 ($= 1 \times 10^6$) cells.

New claims 124-140 depend from or incorporate the limitations of claim 123 and are similar to dependent claims which are pending in the case. Particular support for the limitations can be found in the specification, for example, as indicated in the table below, which is provided for the convenience of the Examiner.

New Claim	Similar to Pending Claim	Support, for example, in specification on:
124	104	page 20, lines 5-10
125	105	page 20, lines 5-7
126	106	page 25, lines 26-28
127	107	page 25, lines 28-30
128	108 (as currently amended)	page 25, line 34 to page 26, line 1
129	109	original claims 14 and 28
130	112	page 21, lines 9-12
131	113	page 21, line 18 to page 22, line 1
132	115	page 5, lines 27-35 and page 12, lines 2-5[8]
133	116	page 19, lines 27-31 and page 40, lines 25-28
134	94	page 12, lines 10-13; page 33, lines 14-16; page 34, lines 11-14; page 38, lines 4-25; working Example 3 beginning on page 65 through page 73; and data shown in Figures 12 A-D, 13 A-D, and 15 A-B
135	95	page 38, lines 4-25; working Example 3 beginning on page 65 through page 73; and data shown in Figures 12 A-D, 13 A-D, and 15 A-B
136	118	page 36, lines 20-22[8]
137	119	page 36, lines 22-24

[8] See also previous paper filed by Applicants and subsequent Action, in which previous rejection was overcome.

New claims 138 and 140 require that the culture medium of claim 123 and 101, respectively, further comprises TNF-α. Support for this limitation can be found in the specification, for example, on page 27, lines 1-19. New claims 139 and 141 depend from new claim 138 and 140, respectively, and require that the culture medium comprises TNF-α at a particular concentration; support for this limitation can be found in the specification, for example, on page 27, line 10.

The Claims Meet the Requirements of 35 U.S.C. §112, Second Paragraph

The Office Action (page 6, #11) has rejected claim 122 as being indefinite due to being a duplicate of claim 84. Applicants note that, as discussed in the previously submitted Amendment (of March 10, 2s006), claim 122 was added in an attempt to clarify the status of the subject matter of claim 84. In view of the rejoinder of claim 84 with the pending claims (Office Action of 26 May 2006, page 2), claim 122 has been cancelled. Accordingly, this rejection of claim 122 has been obviated by amendment and should be withdrawn.

The Rejection of Claims under 35 U.S.C. § 102(a) Should Be Withdrawn

The Office Action (page 6, #13) has rejected claims 84-86, 89, 91-92, 94-95, 99, 101, and 103-122 under 35 U.S.C. § 102(a) over Pancholi *et al.* (1992) *Immunology* 76: 217-224. Claims 114 and 122 have been canceled. Applicants respectfully disagree with this conclusion and traverse the rejection with regard to the remaining claims.

Particularly, Applicants note that the Pancholi reference was published in June 1992, several months after the priority date of the present application and therefore should not be citable against the present claims under 35 U.S.C. § 102(a). Accordingly, Applicants respectfully submit that this rejection of claims be withdrawn.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully submit that all rejections have been overcome and that the claims are in condition for allowance. However, if the Examiner believes that any further discussion of this communication would be helpful, he is encouraged to contact the undersigned by telephone.

No additional fees or extensions of time are believed to be due in connection with this communication except for those indicated in documents accompanying this paper. However, if any additional extensions of time are necessary for the consideration of this paper, such extensions are petitioned under 37 CFR § 1.136(a). Please apply any charges that may be due for extensions of time or for net addition of claims to our Deposit Account No. 50-3187.

Respectfully submitted,

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